In th Claims:

Please amend the claims as follows:

1. (Original) A BACE protein, which comprises the sequence set out in residues 45 to 455 of SEQ ID NO:2 (43 to 453 SwissProt P56817), or a fragment thereof comprising residues corresponding to 58 to 398 of SEQ ID NO:2, modified by the following changes:

substitution or deletion of at least one residue which is a proteolytic cleavage site recognised by clostripain; and optionally

the replacement of from 1 to 30 other amino acids by an equivalent or fewer number of amino acids.

2. (Original) A protein according to claim 1 wherein at least one of residues 44, 47, 57, 58 and 59 of SEQ ID NO:2 are substituted.

3. (Original) A protein according to claim 1 wherein residues 58 and/or 59 are lysine.

4. (Original) A protein according to claim 1 wherein the asparagine residues at positions 155, 174, 225 and 356 (SwissProt P56817 153, 172, 223 and 354) are replaced by glutamine residues.

5. (Original) A protein according to claim 1 wherein the fragment is truncated at the C-terminus such that at least residues 449 *et seq.* of SEQ ID NO:2 are absent.

6. (Original) A method of making a truncated BACE protein, which method comprises proteolytically cleaving the protein of claim 1.

7. (Original) The method of claim 6 wherein said cleavage is at and includes one or more of residues 44, 47, 57, 58 and 59.

8. (Original) A BACE protein obtained or obtainable by the method of claim 7.

9. (Original) A protein according to claim 8 wherein the N-terminal is residue 45 of SEQ ID NO:2.

10. (Currently Amended) A protein according to claim 1 which is selected from: (a) SEQ ID NO: 6; (b) SEQ ID NO: 8; (c) SEQ ID NO: 10; (d) SEQ ID NO: 12; (e) SEQ ID NO: 14; (f) SEQ ID NO: 16; (g) SEQ ID NO: 18; or a truncated BACE protein obtainable by a method comprising proteolytically cleaving the protein of claim 1, wherein said cleavage is at and includes one or more of residues 44, 47, 57, 58, and 59, wherein the protein is selected from (h) SEQ ID NO: 19; (i) SEQ ID NO: 20; (j) SEQ ID NO: 21.

11. (Original) A nucleic acid encoding the protein of claim 1.

12. (Original) A vector comprising the nucleic acid of claim 11.

13. (Original) A host cell comprising the vector of claim 12.

14. (Original) A process for producing the protein of claim 1 comprising the steps of: (a) culturing a host cell comprising a vector comprising a nucleic acid encoding the protein of claim 1 under conditions suitable for expression of the protein; and optionally (b) isolating the expressed recombinant BACE protein.

15. (Original) A process for producing refolded recombinant BACE protein comprising the steps of: (a) solubilising the recombinant BACE; (b) diluting the solubilised BACE into an aqueous buffer containing 10 to 50 mM sulfobetaine; and (c) maintaining the diluted solution at low temperature and at high pH for at least 2 weeks.

16. (Original) A process for producing a crystal of BACE comprising the step of refolding recombinant BACE protein according to the process of claim 14.

17. (Original) A process for producing a crystal of a BACE protein comprising the step of growing the crystal by vapour diffusion using a reservoir buffer that contains 18-26 % PEG 5000 MME, 180-220 mM ammonium iodide and 180-220 mM tri-sodium citrate pH 6.4-6.6, and optionally 0-5% glycerol.

18. (Original) A process according to claim 15 wherein the BACE protein is human BACE.

19. (Original) A process according to claim 17 wherein the BACE protein is human BACE.

20. (Original) A process according to claim 15 wherein the BACE protein is as defined in claim 1.

21. (Original) A process according to claim 17 wherein the BACE protein is as defined in claim 1.

22. (Original) A crystal of a BACE protein having a hexagonal space group $P6_122$.

23. (Original) The crystal of claim 22 having unit cell dimensions of a=b=103.2 Å, c=169.1 Å, $\alpha=\beta=60°$, $\gamma=120°$, and a unit cell variability of 5% in all dimensions.

24. (Original) A crystal of a BACE protein comprising a structure defined by all or a portion of the co-ordinates of Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å.

25. (Original) A crystal of the protein of claim 1.

26. (Original) The crystal of claim 22 having a resolution better than 2.5 Å.

27. (Original) The crystal of claim 24 having a resolution better than 2.5 Å.

28. (Original) The crystal of claim 22 which is soaked with one or more compound(s) to form co-complex structures.

29. (Original) The crystal of claim 24 which is soaked with one or more compound(s) to form co-complex structures.

30. (Original) The crystal of claim 22 wherein the BACE is co-crystallized with one or more compound(s) to form co-crystallized structures.

31. (Original) The crystal of claim 24 wherein the BACE is co-crystallized with one or more compound(s) to form co-crystallized structures.

32. (Original) The crystal of claim 22 which is an apo crystal.

33. (Original) The crystal of claim 24 which is an apo crystal.

34. (Original) A computer-based method for the analysis of the interaction of a molecular structure with a BACE protein, which comprises:

(a) providing a structure comprising a three-dimensional representation of BACE or of a portion of BACE, which representation comprises all or a portion of the coordinates of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(b) providing a molecular structure to be fitted to said BACE structure; and

(c) fitting the molecular structure to the BACE structure of (a).

35. (Original) The method of claim 34 wherein the molecular structure to be fitted is in the form of a model of a pharmacophore.

36. (Original) The method of claim 34 wherein the three-dimensional representation is a model constructed from all or a portion of the coordinates of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å.

37. (Original) The method of claim 36 wherein the model is: (a) a wire-frame model; (b) a chicken-wire model; (c) a ball-and-stick model; (d) a space-filling model; (e) a stick-model; (f) a ribbon model; (g) a snake model; (h) an arrow and cylinder model; (i) an electron density map; (j) a molecular surface model.

38. (Original) A computer-based method for the analysis of molecular structures which comprises:

(a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å ("selected coordinates");

(b) providing the structure of a molecular structure to be fitted to the selected coordinates; and

(c) fitting the structure to the selected coordinates of the BACE structure.

39. (Original) The method of claim 38 wherein the selected coordinates are of at least 5, 10, 50, 100 or 500 atoms.

40. (Original) The method of claim 34 wherein the coordinates of Table 1 represent a binding pocket.

41. (Original) The method of claim 38 wherein the coordinates of Table 1 represent a binding pocket.

42. (Original) The method of claim 40 wherein the coordinates of Table 1 comprise those relating to residues SER71, GLY72, LEU91, ASP93, GLY95, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368 (based on the numbering of SwissProt P56817).

43. (Original) The method of claim 41 wherein the coordinates of Table 1 comprise those relating to residues SER71, GLY72, LEU91, ASP93, GLY95, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368 (based on the numbering of SwissProt P56817).

44. (Original) A computer-based method of rational drug design comprising the method of claim 28.

45. (Original) A computer-based method of rational drug design comprising the method of claim 38.

46. (Original) A computer-based method of rational drug design comprising comprising:

(a) providing the coordinates of at least two atoms of a BACE structure as defined in Table 1 $\pm$ a root mean square deviation from the Cα atoms of less than 0.5Å ("selected coordinates");

(b) providing the structures of a plurality of molecular fragments;

(c) fitting the structure of each of the molecular fragments to the selected coordinates; and

(d) assembling the molecular fragments into a single molecule to form a candidate modulator molecule.

47. (Original) A method for identifying a candidate modulator of BACE comprising the steps of:

(a) employing a three-dimensional structure of BACE, at least one sub-domain thereof, or a plurality of atoms thereof, to characterise at least one BACE binding cavity, the three-dimensional structure being

defined by atomic coordinate data according to Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å; and

(b) identifying the candidate modulator by designing or selecting a compound for interaction with the binding cavity.

48. (Original) The method of claim 34 further comprising the step of:

(a) obtaining or synthesising the molecular structure or modulator; and

(b) contacting the molecular structure or modulator with BACE to determine the ability of the molecular structure or modulator to interact with BACE.

49. (Original) The method of claim 38 further comprising the step of:

(a) obtaining or synthesising the molecular structure or modulator; and

(b) contacting the molecular structure or modulator with BACE to determine the ability of the molecular structure or modulator to interact with BACE.

50. (Original) The method of claim 46 further comprising the step of:

(a) obtaining or synthesising the molecular structure or modulator; and

(b) contacting the molecular structure or modulator with BACE to determine the ability of the molecular structure or modulator to interact with BACE.

51. (Original) The method of claim 47 further comprising the step of:

(a) obtaining or synthesising the molecular structure or modulator; and

(b) contacting the molecular structure or modulator with BACE to determine the ability of the molecular structure or modulator to interact with BACE.

52. (Original) A method of assessing the ability of a candidate modulator to interact with BACE which comprises the steps of:

(a) obtaining or synthesising said candidate modulator;

(b) forming a crystallized complex of a BACE protein of claim 1 and said candidate modulator; and

(c) analysing said complex by X-ray crystallography or NMR spectroscopy to determine the ability of said candidate modulator to interact with BACE.

53. (Original) A method for determining the structure of a compound bound to BACE, said method comprising:

(a) mixing BACE with the compound to form a BACE-compound complex;

(b) crystallizing the BACE-compound complex; and

(c) determining the structure of said BACE-compound(s) complex by reference to the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å.

54. (Original) A method for determining the structure of a compound bound to BACE, said method comprising:

(a) providing a crystal of BACE;

(b) soaking the crystal with one or more compound(s) to form a complex; and

(c) determining the structure of the complex by employing the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å.

55. (Original) A method of determining the three dimensional structure of a BACE homologue or analogue of unknown structure, the method comprising the steps of:

(a) aligning a representation of an amino acid sequence of the BACE homologue or analogue with the amino acid sequence of the BACE of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å to match homologous regions of the amino acid sequences;

(b) modelling the structure of the matched homologous regions of said target BACE of unknown structure on the corresponding regions of the BACE structure as defined by Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å; and

(c) determining a conformation for the BACE homologue or analogue which substantially preserves the structure of said matched homologous regions.

56. (Original) A method of providing data for generating structures and/or performing rational drug design for BACE, BACE homologues or analogues, complexes of BACE with a potential modulator, or complexes of BACE homologues or analogues with potential modulators, the method comprising (i) establishing communication with a remote device containing computer-readable data comprising at least one of:

(a) atomic coordinate data according to Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å, said data defining the three-dimensional structure of BACE, at least one sub-domain of the three-dimensional structure of BACE, or the coordinates of a plurality of atoms of BACE;

(b) structure factor data for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(c) atomic coordinate data of a target BACE homologue or analogue generated by homology modelling of the target based on the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(d) atomic coordinate data of a protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å; and

(e) structure factor data derivable from the atomic coordinate data of (c) or (d); and

(ii) receiving said computer-readable data from said remote device.

57. (Original) A computer system containing one or more of:

(a) atomic coordinate data according to Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å, said data defining the three-dimensional structure of BACE or at least selected coordinates thereof;

(b) structure factor data (where a structure factor comprises the amplitude and phase of the diffracted wave) for BACE, said structure factor data being derivable from the atomic coordinate data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(c) atomic coordinate data of a target BACE protein generated by homology modelling of the target based on the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å;

(d) atomic coordinate data of a target BACE protein generated by interpreting X-ray crystallographic data or NMR data by reference to the data of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å; or

(e) structure factor data derivable from the atomic coordinate data of (c) or (d).

58. (Original) The computer system of claim 57 comprising: a computer-readable data storage medium comprising data storage material encoded with the computer-readable data;

(a) a working memory for storing instructions for processing said computer-readable data; and

(b) a central-processing unit coupled to said working memory and to said computer-readable data storage medium for processing said computer-

readable data and thereby generating structures and/or performing rational drug design.

59. (Original) A method for determining the structure of a protein, which method comprises: providing the co-ordinates of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å, and either

(a) positioning the co-ordinates in the crystal unit cell of said protein so as to provide a structure for said protein or

(b) assigning NMR spectra Peaks of said protein by manipulating the coordinates of Table 1 ± a root mean square deviation from the Cα atoms of less than 0.5Å.

60. (Original) A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of claim 34, and admixing the molecule with a carrier.

61. (Original) A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of claim 38, and admixing the molecule with a carrier.

62. (Original) A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of claim 46, and admixing the molecule with a carrier.

63. (Original) A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of claim 47, and admixing the molecule with a carrier.

64. (Original) A method of preparing a composition comprising identifying a molecular structure or modulator according to the method of claim 52, and admixing the molecule with a carrier.

65. (Original) A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or modulator according to the method as defined claim 34; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

66. (Original) A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or modulator according to the method as defined claim 38; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

67. (Original) A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or

modulator according to the method as defined claim 46; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

68. (Original) A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or modulator according to the method as defined claim 47; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

69. (Original) A process for producing a medicament, pharmaceutical composition or drug, the process comprising: (a) identifying a molecular structure or modulator according to the method as defined claim 52; and (b) preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

70. (Original) A process according to claim 65 which further comprises optimising the structure of the modulator molecule; and preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

71. (Original) A process according to claim 66 which further comprises optimising the structure of the modulator molecule; and preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

72. (Original) A process according to claim 67 which further comprises optimising the structure of the modulator molecule; and preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

73. (Original) A process according to claim 68 which further comprises optimising the structure of the modulator molecule; and preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

74. (Original) A process according to claim 69 which further comprises optimising the structure of the modulator molecule; and preparing a medicament, pharmaceutical composition or drug containing the optimised modulator molecule.

75. (Original) A compound identified, produced or obtainable by the process or method of claim 34.

76. (Original) A compound identified, produced or obtainable by the process or method of claim 38.

77. (Original) A compound identified, produced or obtainable by the process or method of claim 46.

78. (Original) A compound identified, produced or obtainable by the process or method of claim 47.

79. (Original) A compound identified, produced or obtainable by the process or method of claim 52.

80. (Original) A compound of claim 75 or composition thereof for use in medicine.

81. (Original) A compound of claim 76 or composition thereof for use in medicine.

82. (Original) A compound of claim 77 or composition thereof for use in medicine.

83. (Original) A compound of claim 78 or composition thereof for use in medicine.

84. (Original) A compound of claim 79 or composition thereof for use in medicine.